NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2003

PLAN FOR HIV-RELATED RESEARCH

IV: THERAPEUTICS

PREPARED BY THE OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Therapeutics

SCIENTIFIC ISSUES

The ongoing research on the pathogenesis and treatment of HIV disease, and its manifestations, continues to provide important insights that have led to the development of potent antiretroviral therapies. Use of such therapies continues to result in the significant reduction of the viral load in patients who can adhere to, as well as tolerate, these therapies. However, the improvements associated with these therapies, such as reduced viral load, increased CD4 cell counts, decreased opportunistic infection (OI) rates, and improved immune function are also associated with significant toxicity. An ever-increasing appreciation for the range and types of toxicities requires the identification of therapeutic regimens that are less toxic, promote easier adherence, limit the development of drug resistance, enter viral reservoirs to inhibit viral replication, and are more readily accessible. The latter continues to be an urgent need, given the inexorable progression of the pandemic and its impact in the developing world. The scientific agenda for this area of research is focused upon answering the following questions:

- Are there new viral and cellular targets against which therapies can be directed?
- What therapeutic agents can be developed that target drug resistant virus and have activity in viral compartments and cellular reservoirs?

- What are the optimal therapeutic approaches to the management of HIV infection, including when to start, change, or sequence therapy?
- How can the pharmacologic properties of these agents be improved?
- What are the pharmacokinetics of these drugs in pregnant and breast-feeding women, and what impact does this have upon the fetus?
- What are the markers to predict the efficacy of immune-based therapies?
- What is the impact of co-infection upon disease progression and treatment of both HIV and the co-existing infection, such as hepatitis B (HBV), hepatitis C (HCV), tuberculosis (TB), or malaria?
- What are the clinical and public health ramifications of antiretroviral treatment in developing countries?
- What types of interventions facilitate the delivery of therapeutic interventions for HIV disease in a resource-poor setting?

PRECLINICAL DEVELOPMENT OF NEW THERAPEUTIC AGENTS

PRIORITIES FOR FUTURE RESEARCH:

- **Advance the discovery and validation of new viral and cellular targets.**
- **Develop new therapeutic agents that:**
  - **target drug-resistant virus;**
  - **have activity in viral compartments and cellular reservoirs; and**
  - **have improved pharmacologic properties.**
- **Develop *ex vivo* and/or animal models to evaluate the biological properties of drugs, including their pharmacology and toxicology.**

The discovery and validation of new viral and cellular targets to direct the development of new therapeutic agents is a priority for NIH-sponsored research. Continued advances in therapeutics research demonstrates the need for ongoing Government- and industry-sponsored drug development research, preclinical development of new agents, and clinical trials. The goal of this work is not only to slow disease progression, but also to improve the quality of life and extend life expectancy for HIV-infected individuals in both developed and developing countries. NIH sponsors an active and comprehensive drug discovery and drug development program that permits the design and identification of new, safe, and more effective drugs that target drug resistant virus, have activity in viral reservoirs

and cellular compartments, and have improved pharmacologic properties. With the development of *ex vivo* and/or animal models to evaluate the biological properties of these drugs (including their pharmacology and toxicology), better understanding of their potential role in the treatment armamentarium can be appreciated. The increased role of toxicities in significant morbidity, decreased quality of life, as well as interruption of therapies demonstrates the importance of these models.

NIH-sponsored programs provide resources for conducting preclinical testing of potential compounds against HIV infection and its sequelae. The identification of new viral and cellular targets is key if significant gains are to continue in treatment options and modalities. The toxicities associated with current therapies and their impact upon adherence, quality of life, and attendant morbidities make *ex vivo* and/or animal models to evaluate these new agents particularly important. Additional efforts are essential to accelerate the development and testing of microbicides and of other chemical and physical barriers to halt the sexual transmission of HIV and STDs. A separate component of this Plan has been developed for this crucial area of NIH-sponsored research. Coordination of and collaboration between Government-sponsored programs and the pharmaceutical and biotechnology industries is essential to advancing potential agents through this stage of drug development.

PERINATAL TRANSMISSION INTERVENTION

PRIORITIES FOR FUTURE RESEARCH:

- **Develop therapeutic regimens to block perinatal transmission that can be implemented in developed and developing nations. Develop safe, effective, feasible, and conveniently administered strategies to interrupt maternal-fetal transmission of HIV.**
- **Evaluate the safety and pharmacokinetics of antiviral agents in pregnant and breast-feeding women, including studies on the transplacental passage of the agents and safety for the fetus.**
- **Evaluate pharmacokinetics, metabolism, tissue absorption, and drug elimination in the newborn.**
- **Conduct studies to evaluate and reduce short- and long-term toxicity of antiretroviral drugs in women during pregnancy, and their children who were perinatally exposed.**

Further attention to the development and testing of interventions to halt perinatal transmission is also necessary. Despite success in many settings, mother-to-child transmission continues to be a significant problem in developing countries and resource-poor settings. Advances in the

knowledge of not only pharmacologic interventions, but also the impact of such interventions upon the fetus, the short- and long-term toxicity potential, and the transplacental passage of the agents are needed.

Since the success of the initial Pediatric AIDS Clinical Trials Group Protocol 076 in the reduction of perinatal transmission with zidovudine chemoprophylaxis, substantial advances have been made in the treatment, monitoring, and understanding of HIV infection. However, despite these gains, there are many considerations in the treatment of HIV infection during pregnancy, and the data to address these considerations are not yet available. Some of these issues include the pharmacokinetics of antiviral agents in pregnant and breast-feeding women, as well as the transplacental passage of these agents. Several preliminary studies suggest that the placental levels of these drugs may be higher (or lower) than maternal blood levels. The consequences of these levels, how drug dosing should be adjusted, and the short- and long-term consequences of these findings is unknown.

Of equal importance is that the majority of perinatal HIV infections are occurring in the developing world, where a complex array of challenges have delayed widespread use of antiviral agents to prevent transmission. Regimens that are safe, effective, feasible, and convenient are desperately needed to block perinatal transmission in resource-poor settings. An important area of study is the potential short- and long-term toxicities of these agents in both HIV-infected and uninfected children exposed perinatally to antiretroviral drugs.

DEVELOPMENT OF IMMUNOLOGY THERAPEUTICS

PRIORITIES FOR FUTURE RESEARCH:

- **Develop and evaluate therapeutic approaches that will improve and sustain immune function.**
- **Identify and validate markers to predict the efficacy of immune-based therapies.**

During the initial burst of viral activity after HIV infection, high levels of viral replication occur. Recent studies conducted domestically, as well as internationally, have provided additional insights into the pathogenesis of HIV infection and into the role of the individual immune factors in containing the infection (virologic set point). While the initiation of highly active antiretroviral therapy (HAART) has afforded great improvements with restoration of immune function, as well as improved immunologic parameters, further study is needed to determine what therapeutic approaches can improve and sustain immune function. Similarly, the identification of markers that will predict the efficacy of immune-based therapies is needed.

CLINICAL EVALUATION OF THERAPIES

PRIORITIES FOR FUTURE RESEARCH:

- **Determine optimal therapeutic strategies including when to start, change, sequence, or "interrupt" therapies.**
- **Target populations, especially women, injecting drug users (IDUs), children, adolescents, older adults, and across racial/ethnic groups.**
- **Identify regimens with improved toxicity, efficacy, pharmacokinetics, activity in viral reservoirs, and adherence potential.**
- **Enhance capabilities for long-term follow-up and evaluate the long-term effects of therapy including delayed or late toxic effects.**

The introduction of HAART has had a significant impact upon quality of life, immune restoration, life expectancy, and survival. Despite their significant toxicities, these therapies have altered not only the course of HIV infection, but also the perception of HIV infection. However, as the AIDS epidemic continues inexorably into disenfranchised and marginalized communities such as racial and ethnic minorities, the poor, and substance and alcohol abusers, there persists a need to recruit and retain such individuals in clinical trials. Increasing rates of HIV infection at both ends of the age spectrum—adolescents and older Americans—require that these populations be increasingly reflected in NIH-sponsored research in numbers that reflect the ongoing epidemic. Renewed efforts to reach this goal remain an important focus of NIH-sponsored clinical trials.

The identification through such clinical trials of effective treatment regimens with decreased toxicity, increased efficacy, and pharmacokinetics that facilitate adherence will also be important. The metabolic and morphologic alterations associated with these therapies present significant morbidity and warrant further exploration, especially to determine if gender and/or racial differences affect the manifestation, presentation, or severity of these toxicities. Increased activity of drug regimens in viral reservoirs is needed as one of many approaches to decrease viral resistance. Finally, determining the optimum therapeutic strategy, including when to start, when to switch, as well as if and when to interrupt, are important and incompletely answered questions.

EVALUATION OF CO-INFECTION

PRIORITIES FOR FUTURE RESEARCH:

- **Evaluate the effect of co-infection especially with HBV, HCV, or TB on the management of HIV. Determine the bidirectional effects of co-infection and treatments on disease progression and drug interactions.**

- **Develop new agents for the treatment of HBV, HCV, and TB in the setting of HIV infection, with specific attention to pharmacologic drug interactions and non-overlapping toxicity.**

Rates of HCV infection continue to increase rapidly, and the continued expansion of the AIDS epidemic into the substance abuse and minority communities means greater numbers of co-infected persons. Greater understanding is needed to determine the bidirectional effects of co-infection, and treatments for these co-infections, upon disease progression and drug interactions. In addition, hepatitis, tuberculosis, and malaria continue to play a significant role as co-morbidities in HIV infection internationally. New agents are needed for the treatment of HBV, HCV, and TB in the setting of HIV infection, with particular attention to drug interactions and minimizing toxicities.

INTERNATIONAL

PRIORITIES FOR FUTURE RESEARCH:

- **Expand international clinical research programs in countries with limited resources.**
- **Evaluate the clinical and public health impact of prophylactic and therapeutic interventions for co-infections/OIs.**
- **Evaluate the clinical and public health impact of antiretroviral treatment.**
- **Design studies to improve and facilitate the delivery of therapeutic interventions for HIV disease.**

The global nature of the pandemic requires that treatment be viewed in the context of a myriad of potentially mitigating factors: resources available, infrastructure to deliver these therapies, co-existing infections, and public health impact. While a significant challenge, therapeutic developments must be targeted to all who are impacted by HIV infection.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Identify and validate viral and cellular functions required for HIV replication that can be targeted for viral inhibition. Discover and develop novel agents and therapeutic strategies directed against viral and host factors involved in HIV infection and replication.

STRATEGIES:

- Identify, characterize, and validate new and understudied viral and host targets for anti-HIV therapy (e.g., factors involved in viral fusion, entry, integration, transcription, replication, assembly, budding, infectivity, virulence, and pathogenicity). Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - Develop agents (including natural products) and treatment strategies that target and inhibit HIV in cellular, anatomical, and organ reservoirs and sanctuaries.
  - Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
  - Develop new compounds and chemical formulations, including microbicides and other methods, suitable for the genitourinary and gastrointestinal tracts.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent therapeutic agents with activity against drug-resistant strains. Post lead structures to publicly accessible databases in real time.
  - Integrate genomics and informatics paradigms, concepts, and methodologies (microchip-based screens and analyzers) into mainstream drug discovery and development of therapeutic entities and strategies.

- Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; establish the infrastructure to provide services and reagents needed by the scientific community.
- Evaluate the intracellular pharmacokinetics and activity of antiretroviral agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.
- Develop agents with desirable biopharmaceutical characteristics (e.g., improved bioavailability and tissue penetration to the central nervous system [CNS] and other sanctuaries); develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.

- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.
  - Advance basic and applied gene-based strategies to treat HIV infection and its complications. Foster new approaches and technologies to optimize gene delivery that results in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.
  - Develop mathematical and computer models of HIV infection and therapeutic interventions that stimulate and predict *in vivo* efficacy, toxicity, and other outcomes of drug regimens and clinical trials.
  - Investigate the host cell effects of antiretroviral drugs.

OBJECTIVE:

Conduct clinical trials (including the development of new methodologies) to (1) evaluate the short- and long-term safety and efficacy of therapeutic agents and strategies against HIV infection; (2) identify optimal and appropriate treatment modalities in treatment-naive and treatment-experienced HIV-infected individuals; and (3) define, evaluate, and mitigate factors that adversely affect the success of therapeutic strategies against HIV infection. Encourage clinical trial designs that advance the understanding of disease pathogenesis and progression. Develop appropriate partnerships to design and conduct clinical studies domestically and internationally.

STRATEGIES:

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents to determine pharmacokinetics, tissue bioavailability, antiviral activity effects on the immune system, safety, and clinical efficacy.
  - Evaluate optimal combinations of agents selected for antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - Evaluate optimal therapies and strategies for individuals who have acute or recent infection, chronic infection but no prior antiretroviral therapy, and those with prior antiretroviral therapy including patients with multi-drug resistant virus.
  - Support clinical trials to study
    - the long-term efficacy (including toxicities) of therapeutic strategies,
    - the timing, selection, and strategic sequencing of antiretroviral agents to optimize clinical outcome, and
    - the effects of structured treatment interruption on virologic, immunologic, and clinical outcome.
- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials that reflect the demographics of the epidemic, including traditionally underrepresented populations. When appropriate, evaluate potential gender, race, ethnicity, age-specific, and pregnancy-related differences in drug efficacy and safety, including pharmacokinetics, metabolism, tissue absorption, and drug elimination.

- Identify and evaluate the viral and host factors associated with antiretroviral treatment failure including malabsorption, drug interactions, drug resistance, and suboptimal adherence.
- Support clinical trials to evaluate the safety and efficacy of gene therapy.
- Support studies that combine novel therapeutic modalities (e.g., cell-based, gene-based, and therapeutic vaccine approaches) with state-of-the-art antiretroviral therapies.

- Encourage and facilitate the study of co-formulated antiretrovirals. Encourage cooperation of the private sector/industry in this effort.
- Evaluate the benefits or risks of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with antiretroviral therapy.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate the prognostic value of surrogate markers in response to various therapeutic interventions.
- Design, test, and evaluate methods to improve the retention of patients in clinical trials.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of antiretroviral agents.

  Develop methodology to facilitate cross-protocol analysis and meta-analyses.

Pharmacology

- Determine the relationship between drug exposure (pharmacokinetics) and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management.
- Investigate drug interactions among commonly used treatments for HIV-related disease and its complications, as well as other substances that may be used by HIV-infected individuals.

Viral Reservoirs

- Evaluate the presence and persistence of HIV in different tissue compartments during HAART; investigate the role of anatomic and cellular sanctuaries in the development of HIV drug resistance, transmission, and establishment of long-term reservoirs.

Viral Resistance and Fitness

- Explore the utility of real-time antiretroviral phenotypic and genotypic assays in managing antiretroviral therapy across a broad spectrum of patients.
- Evaluate the impact of transmission of drug-resistant HIV strains on disease progression and therapy.

Adherence

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to facilitate better adherence to antiretroviral regimens.
- Develop better methods to assess adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.

Transmission

- Evaluate the role of antiretroviral therapy (or other treatment modalities) administered in the immediate post-HIV-exposure period in the prevention of HIV transmission.
- Conduct clinical testing of microbicidal agents and other chemical and physical barriers to demonstrate safety and efficacy in reducing sexual transmission of HIV.

Co-infection with Hepatitis B and/or C Virus

- Evaluate the bi-directional effects of co-infection with hepatitis B and/or C virus in individuals with HIV. Evaluate the impact of potent antiretroviral therapy in the setting of hepatitis, including reactivation of hepatic viruses, the treatment of viral hepatitis in co-infected patients, and the development of late-stage complications of viral hepatitis.

International

- Enhance the development of international collaborations that will assist in addressing relevant therapeutic research questions by including populations of HIV-infected adults and children from other nations.
- Assist developing nations, as appropriate, in technology transfer to facilitate the evaluation of antiretroviral agents and other therapies in local settings.
- Assess the barriers to delivery of effective HIV/AIDS care and the capability of conducting international therapeutic trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop/expand infrastructures for the conduct of multidisciplinary, international clinical research, including reliable laboratory monitoring services (routine hematologic, immunologic, virologic tests, etc.).

OBJECTIVE:

Develop strategies to evaluate, prevent, and treat antiretroviral therapy-related complications.

STRATEGIES:

- Evaluate potential delayed or late-toxic effects of antiretroviral therapy following short-term administration of prophylaxis regimens as well as during chronic treatment.
- Support research on the pathogenesis and mechanisms of the complications of therapeutic regimens used to treat HIV disease and its associated disorders.
- Develop and test approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which antiviral therapies and/or suppression of HIV replication may affect metabolic processes.
- Integrate metabolic, endocrine, cardiovascular, and bone studies into ongoing and planned treatment trials, including treatment interruption trials, which may provide an opportunity to answer important questions related to potential complications of antiretroviral therapy.

OBJECTIVE:

Identify and validate potential molecular targets for the discovery and development of agents for prevention and treatment of HIV-associated infections. Develop and evaluate new agents and strategies for preventing and treating OIs and other co-infections, especially HBV, HCV, TB, and human papillomavirus (HPV).

STRATEGIES:

- Improve our understanding of the interplay between HIV-associated immune deficits and the onset, as well as types of infectious complications.
  - Develop *in vitro* culture systems for opportunistic microorganisms such as *Pneumocystis carinii*, cryptosporidia, and microsporidia; develop animal models that predict the efficacy of potential agents for preventing and/or treating OIs.
  - Delineate the structure and function of potential molecular targets of HIV-associated opportunistic microorganisms. Support preclinical drug development programs to develop therapies against associated pathogens, especially *Pneumocystis*, Cryptosporidium, *Mycobacterium avium* complex (MAC), *Mycobacterium tuberculosis* (TB), microsporida, JC virus (JCV, the etiologic agent of progressive multifocal leukoencephalopathy [PML]), cytomegalovirus (CMV), HPV, azole-resistant fungi, and other prominent co-infections, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics.
  - Study the complex interaction between HIV infection and OI microorganisms upon pathogenesis, presentation, and disease outcomes in adults and children.
  - Determine the role of preexisting immunity in controlling OIs; evaluate immune-based therapies as adjuncts for treating OIs.
- Support and encourage mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents used for treating OIs; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.
  - Determine the high-resolution molecular structures for proteins from OI microorganisms; utilize these structures in the design of inhibitors; provide coordinates for resolved structures to publicly accessible databases in real time; determine structures of other OI macromolecules as potential targets.

- Conduct clinical trials to evaluate agents for the prophylaxis and treatment of HIV-associated OIs; target OIs shown to cause significant morbidity by epidemiological studies, and made worse by HIV-induced immunosuppression.
  - Conduct preclinical studies of anti-OI drugs (alone or in partnership with industry) to assess their immunologic, pharmacokinetic, pharmacodynamic, toxic, reproductive, and teratogenic effects, as well as transplacental carcinogenicity.
  - Support clinical trials that assess the impact of new antiretroviral regimens on the risks for and manifestations of OIs associated with HIV/AIDS in adults and children.
  - Improve strategies for simultaneous prevention of multiple OIs in the context of antiretroviral treatment; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs; develop improved OI strategies to minimize toxicities and the development of drug-resistant microorganisms.
  - Support clinical research in the context of drug abuse treatment to reduce OIs among HIV-infected drug users; develop and evaluate interventions to facilitate better adherence to therapies among populations with HIV infection and substance abuse and/or mental illness.
  - Support clinical trials, domestic and international, of individuals co-infected with HIV and TB (both active and latent infection). Evaluate safety and efficacy of treatment regimens in co-infected patients. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression (late versus middle versus advanced HIV disease).
  - Evaluate drug interactions between antituberculous agents and HIV medications. Support the investigation of new antituberculous agents with fewer side effects, drug interactions, and/or action against multiple drug-resistant TB (MDR-TB).
  - Support clinical trials investigating the efficacy and risks of treatment of hepatitis C in individuals who are co-infected with HIV and HCV.
  - Support clinical trials to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs in HIV-infected infants, children, and pregnant women.

- Develop tools to identify HIV-infected individuals at high risk for development of specific OIs to improve the efficiency of clinical trial design and the risk/benefit ratio of the currently utilized drugs for prophylaxis and for treatment.
  - Support research on the effectiveness of pharmacologic and other approaches in promoting adherence to anti-OI regimens.
  - Investigate surrogate markers of TB disease that could distinguish between latent, active, and eradicated infection in co-infected individuals.
  - In HIV and TB co-infected individuals, determine how each infection influences or alters the other disease in respect to progression and response to therapy.
  - In HIV and HCV co-infected individuals, determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Study the differential impacts of primary acquisition of OI pathogens compared to reactivation of latent infections on disease manifestations and treatment.
- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs, quantitative assessment of microbiological responses, and drug sensitivity testing of opportunistic microorganisms, especially *M. tuberculosis, M. avium*, enteric pathogens, *P. carinii*, CMV, fungi, toxoplasma, and JCV.
- Develop OI-specific vaccines; determine the ability of HIV-infected adults and children to respond to current and new vaccines against OIs throughout the course of their HIV infection.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-OI drugs appropriate for use in infants, children, and other populations.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of agents used to prevent or treat OIs.
- Cooperate with the private sector to increase involvement and investment in OI drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

OBJECTIVE:

Develop, evaluate, and implement strategies for interrupting vertical transmission of HIV in developed and developing countries. Include studies of strategies to interrupt transmission from breast-feeding; medications including short- and long-term effects; and placental structure and function, and its role in preventing or facilitating HIV transmission.

STRATEGIES:

Mechanisms of Transmission

- Investigate the mechanisms and timing of perinatal HIV transmission (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to further decrease perinatal transmission or provide alternatives to currently identified effective strategies.
- Investigate risk factors for breast milk associated with early and late HIV transmission (e.g., breast milk viral load, immune factors, mastitis, and exclusive versus mixed breast-feeding).
- Evaluate the influence of pre-existing maternal viral drug resistance on the efficacy of antiretroviral regimens to prevent perinatal transmission.
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk.
- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum transmission of lentivirus, and to evaluate transplacental passage of antiretroviral agents and their effects on placental function and on fetal development and viability.

Interventions to Reduce Transmission

- Develop safe and conveniently administered strategies to interrupt mother-to-child transmission of HIV using interventions that are affordable in resource-poor nations, including specific strategies to prevent postnatal transmission of HIV through breast milk.
- Evaluate strategies for reducing perinatal HIV transmission when maternal antepartum and intrapartum antiretroviral therapy is not given or available (e.g., postpartum prophylaxis of the infant only).

- Develop and evaluate strategies for implementation of effective prevention interventions in resource-poor and resource-rich countries.
- Support international collaborative efforts to conduct perinatal trials.
- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring without compromising treatment of the pregnant women; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, vitamin supplementation, HIV vaccines, adjuvants, and virucides, alone or in combination.
- Study the effect of antiretroviral regimens used for maternal health indications on the risk of vertical transmission and other outcomes, including pregnancy outcome.

Issues Related to Antiretroviral Interventions

- Evaluate the toxicities, pharmacokinetics (including transplacental drug transfer to fetus/infant), and antiretroviral activity of new agents, existing agents, and combinations of agents in pregnant women and their neonates.
- Evaluate the risk for the development of maternal virus with antiretroviral drug resistance with use of short and/or longer-course antiretroviral prophylaxis regimens, and its effect on vertical transmission, as well as maternal and infant health.
- Support the long-term follow-up of women treated for HIV infection during pregnancy, particularly those who otherwise could have deferred initiating treatment, or who choose to discontinue treatment after delivery, for durable clinical responses as well as safety evaluations.
- Support the long-term follow-up of children exposed to antiretroviral therapies during pregnancy or postpartum to evaluate possible late effects.
- Evaluate the potential mechanism for possible carcinogenic or mutagenic effects of *in utero* antiretroviral exposure.
- Investigate interactions between HIV therapeutics and drugs of abuse or used in the treatment of drug abuse in pregnant women; evaluate the impact of such interactions on the maintenance of anti-addiction therapy and on vertical transmission of HIV.

Clinical Trials and Other Interventions

- Further evaluate the risks and benefits of cesarean delivery for reducing transmission (e.g., evaluate the risk of postpartum morbidity in infected women with elective cesarean delivery and determine whether the additional benefit of cesarean delivery for preventing transmission accrues in women receiving HAART).

- Support research and development of new clinical trial designs, statistical methodologies and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the treatment of pregnant women and their offspring.

- Develop, incorporate, and validate appropriate quality-of-life parameters and methods to measure antiretroviral drug adherence in clinical trials of HIV-infected pregnant women.

Implementation Issues

- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in resource-poor as well as resource-rich settings to permit the earliest possible determination of HIV infection in infants, and whether antiretroviral and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.

- Evaluate innovative methods, including rapid HIV antibody testing, to identify HIV infection in pregnant women with unknown HIV status who present in labor and to assess the acceptability of such testing and peripartum antiretroviral prophylaxis by these women.

- Conduct clinical, operational, and health services research relevant to improving health outcomes in HIV-infected mothers and their children.

OBJECTIVE:

Develop and evaluate therapeutic approaches that will restore and sustain a competent immune system in HIV-infected individuals.

STRATEGIES:

- Employ approaches to immune restoration in clinical trials; test specific hypotheses of HIV immunopathogenesis.
- Evaluate the capacity of the immune system to maintain or repair itself after maximal effective viral suppression.
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults and children.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, and immunoactive agents to prevent further immune deterioration and to reconstitute deficient immune systems.
- Develop and evaluate active and passive immunotherapeutic approaches for HIV infection and its sequelae.
- Support research on approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular immune elements, including use of expanded peripheral blood T cells, bone marrow, cord blood stem cell transplantation, and thymic transplantation.
- Evaluate the immune system after partial restoration by effective antiretroviral therapy. Define qualitative and quantitative differences between the restored immune system and the native immune system to determine if identified deficiencies can be diminished by immunoactive agents.
- Develop new therapeutic strategies based on gene delivery strategies to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, and stromal elements from destruction by HIV.
- Evaluate the potential to inhibit HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels. Develop agents to block the attachment of HIV to receptors and co-receptors and thus inhibit entry into cells.

- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate markers that may identify individuals at risk for late complications of therapy.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials.
- Evaluate treatment interruption (TI) both to stimulate HIV-specific immune response (Structured Treatment Interruption [STI]) and as an analytic readout of treatment effect (Analytic Treatment Interruption [ATI]).
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies.
- Evaluate immune-based therapies for the purpose of improving HAART-sparing regimens, permitting delay in initiating antiretroviral treatment (ART), or delay in reinitiating ART in regimens of scheduled intermittent therapy (SIT).

OBJECTIVE:

Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system disorders in HIV-infected individuals. Investigate the effectiveness of complementary and alternative medicine therapies in treating HIV-related peripheral neuropathy.

STRATEGIES:

- Develop and evaluate novel strategies and agents, such as neuroprotective agents, that are active against putative pathways of HIV-induced CNS dysfunction in adults and children.
- Develop and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Design and conduct clinical trials addressing nervous system complications of HIV infection in adults and in children.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF], neuroimaging) of treatment effects.
- Develop therapeutic agents to block HIV entry into the CNS and treat HIV in the CNS; evaluate their safety and efficacy in clinical trials.
- Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of antiretroviral drugs into the CNS compartment.
- Develop better strategies to prevent, diagnose, and treat peripheral neuropathies in HIV-infected persons.
- Characterize the CNS pharmacokinetics and pharmacodynamics of antiretroviral drugs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.

- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications, with drug abuse therapies, including psychotropics, antidepressants, and other co-morbid disorders.
- Validate and enhance the efficiency of neuropsychological and neurologic tests performed in the context of clinical trials to identify those tests most capable of determining treatment-related changes in different age and cultural groups.
- Determine the prevalence, causes, and pathogenesis of pain in HIV-infected individuals and develop optimal therapies to control pain.
- Monitor CSF for HIV viral load and immune activation markers in patients enrolled in studies of HAART.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease in the setting of clinical trials.
- Support the research and development of new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers, to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic complications of HIV disease.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales that are aimed at measuring the impact of the nervous system complications of HIV infection in clinical trials.
- Selectively incorporate neurologic and neuropsychological assessments into other HIV-related clinical trials.

OBJECTIVE:

Discover, develop, and evaluate improved strategies for the assessment, treatment, and prevention of HIV-associated malignancies.

STRATEGIES:

Pathogenesis Research and Preclinical Drug Development

- Identify novel mechanisms and targets (e.g., cytokines, angiogenesis factors, and hormones) for treatment and prevention of HIV-associated tumors such as Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and HPV malignancies, including anogenital dysplasias and cancers; develop new therapeutic strategies based on these findings.
- Develop *in vitro* models of KS and assays for angiogenesis inhibitors.
- Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles.
- Based upon structural biologic and biochemical information, develop therapeutic agents for the treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models (e.g., severe combined immunodeficiency-human [SCID-hu] mice) for the testing of potential therapeutic strategies against HIV-associated malignancies.

Diagnostic Methods

- Improve methods for early diagnosis of malignancies and for early detection of recurrent cancer.

Clinical Evaluation of Therapeutic and Prevention Strategies

- Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8 and Epstein-Barr virus [EBV], HPV, and HBV) in their pathogenesis.
- Evaluate novel approaches for the treatment of HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.

- Support approaches using gene-based technologies, such as tissue array and microarray in targeting treatment of HIV-associated malignancies.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses with clinical benefit; develop a staging system indicative of prognostic response and survival.
- Encourage collaborative studies within clinical trials networks to develop mechanisms for early identification of patients at high risk for malignancy. Develop and assess interventional strategies to reduce the risk or prevent the development of malignancies.
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.
- Encourage clinical studies of HIV-infected patients with non-AIDS-defining malignancies. Evaluate the impact of therapy upon virologic, immunologic, tumor parameters, and drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with therapy, and study the effects of such strategies on virologic and immunologic parameters.
- Study the role of *in utero* exposure to antiretroviral drugs on the risk of later development of tumors, both in uninfected and infected individuals born to HIV-infected women who received antiretroviral drugs during pregnancy.

OBJECTIVE:

Develop and evaluate strategies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome, growth failure, and hematologic, dermatologic, renal, metabolic, pulmonary, cardiac, gastrointestinal, endocrinologic, psychiatric, and oral manifestations.

STRATEGIES:

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection.
- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other complications of HIV disease.
- Evaluate the safety and efficacy of complementary and alternative medicine therapies—including nonpharmacologic interventions such as exercise, nutrition, and sleep cycles—in the management of HIV disease and its complications.
- Evaluate drug interactions with potential clinical significance for patients with HIV infection, particularly the interactions between antiretroviral agents and psychotropic medications; develop strategies to avoid or minimize the clinical impact of these interactions.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

FY 2003 OAR Planning Group for Therapeutics

FY 2003 THERAPEUTICS PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
AVEG/HVTN	AIDS Vaccine Evaluation Group/HIV Vaccine Trials Network
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CBO	community-based organizations
CDC	Centers for Disease Control and Prevention
CFAR	Centers for AIDS Research
CIPRA	Comprehensive International Programs in Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocytes
DC	dendritic cell
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOT	directly observed therapy
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GI	gastrointestinal

GLP/GMP	good laboratory practices/good manufacturing production
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Unviersities
HBV	hepatitis B virus
HCFA	Health Care Financing Administration
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpes virus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IHS	Indian Health Service
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpes virus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium* complex
MCT	mother-to-child transmission
MDR-TB	multiple drug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organizations

NHL	non-Hodgkin's lymphoma
NHP	non-human primate
NIH	National Institutes of Health
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PHS	Public Health Service
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trials
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	Structured Treatment Interruption
TB	tuberculosis
TI	treatment interruption
UNAIDS	United Nations Joint Programme on AIDS
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

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